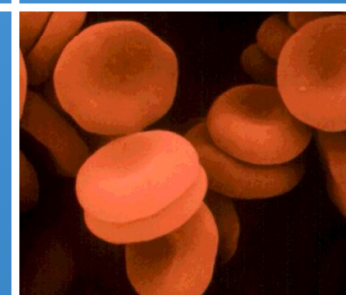
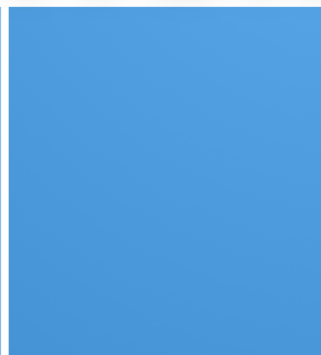
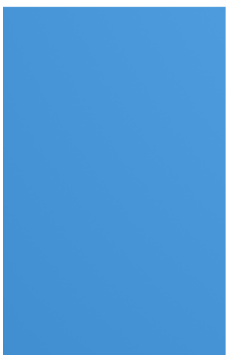


Hematuria



UNDER SUPERVISION OF

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2010

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To all those who have helped us during this research. To ***Dr Nancy Asaad***, Professor of Pathology, to ***Dr Marwa Serag***, Assistant Lecturer of Pathology and to ***Dr Ahmed Khalifa***, Resident of Urology.

We dedicate this work

Research Team

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INTRODUCTION

Hematuria, blood in the urine, is a symptom associated with many diseases rather than being a disease in itself. The cause of hematuria may be as routine as an infection or as serious as cancer.

Hematuria is the topic of this research. We start by talking about *hematuria* and differentiating it from *pseudohematuria*. After that, we will talk about *types and patterns of hematuria*. We will then turn to mention in general some common *causes* of hematuria, from which we will focus on the commonest four causes in Egypt. These are *schistosomiasis*, *urinary stones*, *tumors* and *glomerulonephritis*. At the end, we will give some notes on the *differential diagnosis*, *complications*, *duration* and *treatment* of hematuria. After completing our discussion, we have included *three recently diagnosed clinical cases* associated with hematuria.

We have tried to keep the ideas as clear and as simple as possible. We have done our best to follow the rules of scientific research and writing articles. A lot of time and efforts have been spent to produce this research in this form. We, however, are not sorry and will never be sorry for all this time because we think the experience we have gained and the skills we have learnt are worthy.

We hope we were able to cover the topic from all points of view and could present our research in a good well-organized manner.

Research Team



HEMATURIA

Hematuria is defined as the excretion of abnormal numbers of erythrocytes (either intact or damaged) in the urine ⁽⁹⁾, i.e. more than 5 red blood cells per high-power field in the urinary sediment ⁽¹⁶⁾.

Normal individuals excrete small numbers of erythrocytes in the urine ⁽⁹⁾. Marked variations in the upper limit of normal for urinary RBCs have been reported in normal subjects ⁽²⁷⁾. Approximately 10% of normal subjects will excrete up to 10 erythrocytes/HPF of centrifuged urine sediment. However, less than 3% of normal subjects will excrete more than 3 erythrocytes/HPF ⁽¹⁰⁾. The latter value, three red blood cells per high power field (3 RBCs/HPF), is the most commonly accepted upper limit of normal ⁽²⁷⁾.

When present, hematuria means that something is causing abnormal bleeding in the patient's genitourinary tract. The source of such bleeding can be located anywhere along this tract ⁽³⁴⁾. It may be also a sign of non-urologic systemic disease ⁽¹⁶⁾. So, *hematuria* should always be regarded as a sign of disease originating in the kidneys, of lesions present anywhere along the urinary tract from the renal pelvis to the distal urethra, or as a consequence of a systemic disturbance which has only secondarily affected the kidneys and urinary system ⁽¹⁰⁾.

Hematuria must be distinguished from *pigmenturia* (e.g., hemoglobinuria or myoglobinuria), in which protein or other substances impart an abnormal coloration to urine that resemble hematuria ⁽⁹⁾. This condition is referred to as *pseudohematuria*.



PSEUDOHEMATURIA

The presence of RBCs in urine should be confirmed by microscopic examination to rule out false hematuria⁽²⁴⁾. Some cases that initially present the appearance of gross hematuria turn out to be non-blood related. This condition, called *pseudohematuria*, usually is the result of ingested substances that impart a red color to the urine⁽³⁴⁾.

False hematuria can occur not only in the presence of *free hemoglobin* (hemoglobinuria or myoglobinuria), but also because of *ascorbic acid* (>5 mg per deciliter) or *antiseptic povidone-iodine*⁽²⁴⁾. Excessive consumption of *beets* or *berries*, *food coloring*, *certain laxatives*⁽³⁴⁾, *Rifampicin*⁽²⁸⁾ and *some pain medications* all can result in a pink or reddish cast to the urine⁽³⁴⁾. Many of these substances are delivered to the kidneys from the circulation and are filtered into the urine⁽⁹⁾.

TYPES AND PATTERNS OF HEMATURIA

Three basic groups of terms are used to describe the patterns of hematuria⁽¹⁰⁾.

First, in relation to the color or appearance of the urine, the terms ***gross*** or ***macroscopic*** are used to designate urine which is obviously discolored with blood⁽¹⁰⁾. Hematuria is visible to the naked eye⁽⁹⁾. The urine may even contain small blood clots⁽³⁴⁾. ***Covert*** or ***microscopic*** hematuria refers to urines not distinguishable from normal in gross



appearance but which have abnormal quantities of erythrocytes on microscopic examination ⁽¹⁰⁾. This is because the blood is present in amounts so small that it does not change the color of urine ⁽³³⁾.

Second, the patterns of hematuria with respect to time are described by the use of self-explanatory terms ⁽¹⁰⁾ ***persistent, transient, intermittent*** and ***recurrent*** ⁽⁹⁾.

Finally, the coexistence or absence of symptoms referable to the urinary tract confers the designations of ***symptomatic*** or ***asymptomatic*** (painless) hematuria, respectively ⁽⁹⁾.

These patterns of hematuria may have *diagnostic significance* ⁽⁹⁾ since certain disorders are more likely than others to result in particular patterns with respect to color and appearance, timing, and associated symptoms ⁽¹⁰⁾.

It is important to remember that hematuria in any amount is potentially serious. The amount of blood present does not necessarily indicate the relative seriousness of the underlying problem ⁽³⁴⁾.

CAUSES OF HEMATURIA

Causes of hematuria are multiple ⁽¹⁰⁾ (Table 1). Blood may enter the urine anywhere along the urinary system ⁽³⁰⁾. Abnormal numbers of erythrocytes in the urine may arise from anywhere between the glomerular capillaries and the tip of the distal urethra ⁽¹⁰⁾.



Hematuria may be an early indication of damage or injury to the kidney (s). Some heavy exercise can cause blood to leak into the urine. Blood in the urine is often found in those with a urinary infection or stone. Men who have an enlarged prostate (benign prostatic hyperplasia, BPH) are sometimes found to have blood in the urine. Hematuria may be also a sign of a tumor in the urinary system ⁽³⁰⁾.

According to Dr Ali El-Hindawi ⁽⁵⁾, Causes of hematuria can be classified into *pre-renal*, *renal* and *post-renal* causes.

Pre-Renal Causes of Hematuria (General Causes of bleeding):

- a) *Hypertension*.
- b) *Blood diseases* as leukemia, purpura.
- c) *Vitamin C & K deficiency*.
- d) *Drugs* as salicylates, anticoagulants.

Renal Causes of Hematuria:

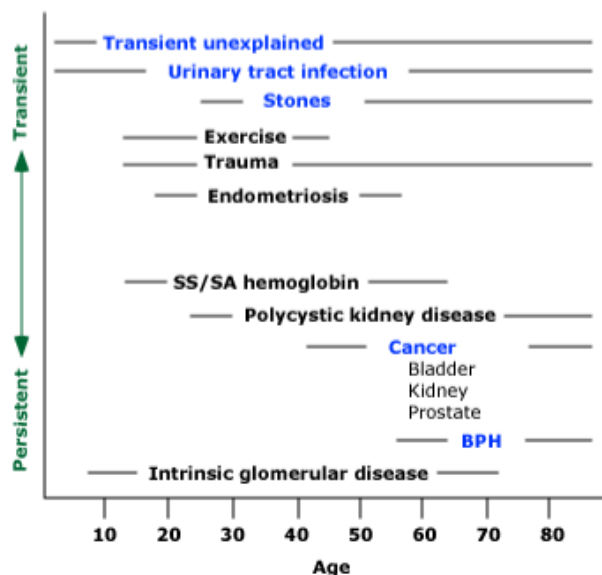
- a) *Congenital* as polycystic kidney.
- b) *Inflammatory* as:
 - a. Nephritic syndrome (as in acute poststreptococcal GN)
 - b. Acute pyelonephritis.
 - c. Renal tuberculosis
- c) *Neoplastic* (renal tumors) as renal cell carcinoma.
- d) *Vascular disorders* e.g. chronic venous congestion and renal infarction
- e) *Traumatic* e.g. kidney injury due to accidents and bleeding following renal surgery. ⁽⁵⁾



Post-Renal Causes of Hematuria

- a) *Congenital* as bladder diverticulum.
- b) *Inflammatory* as:
 - a. Bilharziasis ⁽⁵⁾. Terminal hematuria caused by bilharzial cystitis is the commonest cause of hematuria in Egypt ⁽²⁰⁾.
 - b. Other types of cystitis e.g. acute cystitis, tuberculous cystitis...etc
- c) *Neoplastic* as Tumors of renal pelvis, ureter or bladder (e.g. papilloma, carcinoma...)
- d) Vascular disorders as chronic venous congestion
- e) Traumatic as:
 - a. Traumatic injury by stones. This is a common cause of hematuria.
 - b. Traumatic injury due to instrumentation by metal catheters. ⁽⁵⁾

Figure 1: Major causes of hematuria in relation to age and duration



Schematic representation of the major causes of hematuria in relation to the age at which they usually occur (horizontal axis), transience or persistence (vertical axis), and frequency (blue implies more frequent).

Table 1: Causes of Hematuria

Renal Parenchymal Diseases	Urinary Tract Diseases
Glomerular disease Primary Mesangial IgA nephropathy (Berger's disease) Thin basement membrane nephropathy Mesangial proliferative glomerulonephritis with IgM and/or C3 deposits Membranoproliferative glomerulonephritis Crescentic glomerulonephritis Focal glomerulonephritis Membranous glomerulopathy (<20%) Minimal change disease (<20%) Multisystem Systemic lupus erythematosus nephritis Microscopic polyangiitis Wegener's granulomatosis Henoch- Schönlein purpura Goodpasture's disease Thrombotic microangiopathies (e.g. hemolytic-uremic syndrome) Infection Poststreptococcal glomerulonephritis Infective endocarditis Shunt nephritis Other postinfectious glomerulonephritis Hereditary disease Alport's syndrome Nail-Patella syndrome Fabry's disease Other Primary idiopathic renal hematuria with or without hypercalcauria Vascular and tubulointerstitial diseases Hypersensitivity Acute hypersensitivity interstitial nephritis Tubulointerstitial nephritis with uveitis Neoplastic Tumors (renal cell carcinoma, Wilm's tumor, leukemic infiltrates, angiomyolipoma) Metastatic tumors (uncommon) Hereditary Polycystic kidney disease (autosomal-dominant variety) Medullary sponge kidney Vascular Malignant hypertension Renal arterial emboli or thrombosis Loin pain-hematuria syndrome Arteriovenous malformations Papillary necrosis Analgesic abuse nephropathy Sickle cell trait Diabetes mellitus Alcoholism Ankylosing spondylitis Obstructive uropathy Trauma Acute bacterial pyelonephritis Acquired cystic disease of renal failure and dialysis	Renal Pelvis Transitional cell carcinoma Varices Calculi Trauma Severe hydronephrosis Nevi Ureter Calculi (uric acid, calcium oxalate, calcium phosphate, struvite, cystine, adenine, xanthine, drugs) Transitional cell carcinoma Periureteritis (appendicitis, ileocolitis, abscess) Retroperitoneal fibrosis Ureterocele Varices Endometriosis Tuberculosis Bladder Carcinoma of the bladder Cystitis (bacterial, viral, parasitic, fungal) Chronic interstitial cystitis (Hunner's ulcers) Schistosoma haematobium Radiation cystitis Nitrogen mustard or cyclophosphamide cystitis Hypersensitivity (allergic) cystitis Bladder calculi Sudden decompression of severe overdistention Foreign bodies Vascular anomalies Amyloidosis Trauma Jogger's or marathon runner's hematuria Tuberculosis Prostate Benign prostatic hypertrophy Carcinoma of the prostate Acute or chronic prostatitis Urethra Meatal ulcers Urethral prolapsed Urethral caruncle Acute or chronic urethritis Carcinoma of the urethra or penis Vascular anomalies Trauma Foreign body Condyloma acuminatum Other (endometriosis) In association with a systemic coagulation disturbance (with or without diseases previously listed) Platelet defect Idiopathic or drug induced Thrombocytopenic purpura Thrombasthenia Bone marrow diseases Coagulation protein deficiency Hemophilia A or B Heparin therapy Warfarin therapy Other congenital and acquired defect in coagulation Other Scurvy Hereditary telangiectasia Surreptitious (malingering)

From Glasscock R. Hematuria and pigmenturia. In Massry SG, Glasscock RJ: Textbook of nephrology, 3rd ed. Baltimore, Williams & Wilkins, 1995

SCHISTOSOMIASIS AND HEMATURIA

Schistosomiasis is one of the most significant parasite diseases of humans ⁽²⁹⁾. In 1993, the World Health Organization estimated that at least 200 million people in 74 countries were infected ^{(23) (29)} and 200,000 died per year as reported in 2004 ⁽³⁾. In Egypt, the disease is a major public health problem especially in rural areas with almost six millions Egyptian infected ⁽²⁹⁾.

Different types of schistosomiasis are present. In this part, we will we deal with schistosomiasis caused by *S. haematobium* which is mainly manifested by hematuria.

Egyptians have had a long history of symptoms caused by schistosomiasis, notably hematuria, which appeared classically in young boys and was once deemed to be a sign of puberty ⁽²⁹⁾.

S. haematobium affects primarily the lower urinary tract. Adult worms of this species live in the vesical vasculature. The eggs are laid in the mucosa and submucosa of the urinary bladder and the lower parts of the ureters ⁽²³⁾ around which granuloma and fibrosis are formed ⁽¹²⁾.

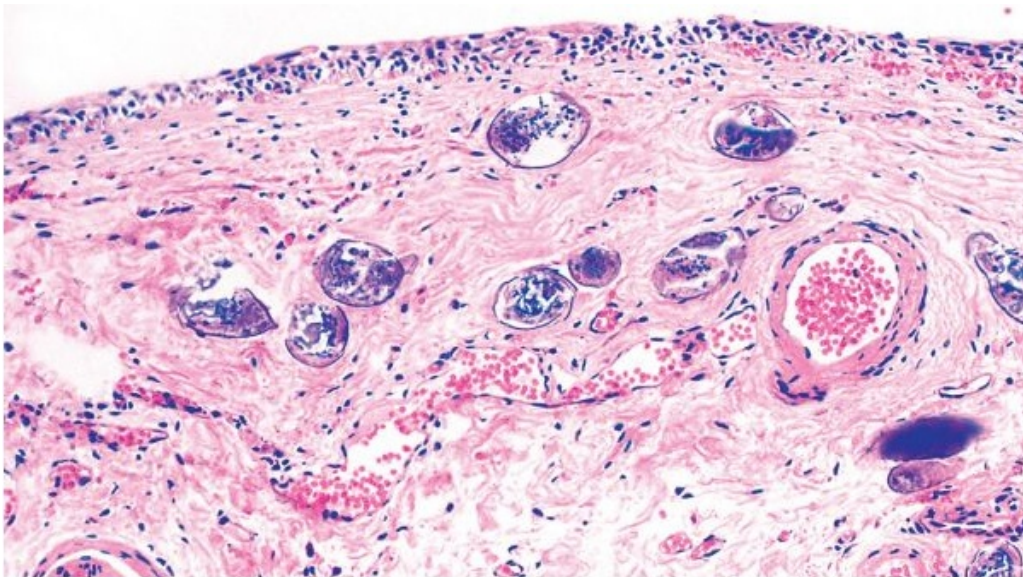
The eggs release protease enzyme ⁽¹²⁾ and a variety of antigenic macromolecules (mostly glycoproteins) ⁽²³⁾ eliciting prominent inflammatory reaction ⁽¹²⁾. This inflammatory reaction is necessary for passive transfer of egg across the bladder wall allowing the eggs to be shed in urine ⁽¹²⁾. The natural course of the ova deposited in the bladder wall is to escape into the bladder cavity especially at the end of



micturition causing *terminal hematuria* ⁽¹⁹⁾. Rather than being excreted, however, some of the eggs may lodge in the tissues of the host. It is the presence of these retained eggs, rather than the worms themselves, that causes the pathology of schistosomiasis ⁽²⁹⁾.

Eggs lodged in mucosa or submucosa of the bladder ⁽²⁹⁾ induce a T lymphocyte-dependent granulomatous response ⁽²³⁾, which may extend into the bladder lumen as polyp ⁽²⁹⁾.

Figure 2



Schistosoma haematobium infection of the bladder with numerous calcified eggs and extensive scarring

Granuloma formation around schistosome eggs has been considered to be *delayed type hypersensitivity* ⁽²⁹⁾. The pathogenesis starts by *miracidia* of the trapped ova that produce "egg antigen" leading to sensitization of T lymphocytes ⁽⁴⁾. The sensitized T helper cell response in this early stage is dominated by TH1 cells that produce IFN- γ , which stimulate macrophages to secrete high level of cytokines TNF, IL-1 and IL-6 that cause fever ⁽¹²⁾. In the chronic stage, TH2 is stimulated.

This causes mast cell to produce IL-4, which induce further TH2 differentiation ⁽¹²⁾ and stimulate IgE production or eosinophilia respectively ⁽²⁹⁾. IL-13 produced by TH2 cells, increases fibrosis by stimulation of the synthesis of collagen ⁽¹²⁾.

Prolonged and severe infection results in gross lesions in the form of sandy patches, polyp, ulcers and epithelial changes ⁽¹⁹⁾.

Sandy patches are common ⁽¹⁹⁾. They develop by deposition of large number of eggs, followed by atrophy of the mucosa due to vascular compression ⁽⁴⁾. The mucosa shows dirty yellow raised patches. The epithelium is atrophic and covers a fibrotic submucosa packed with calcified ova ⁽¹⁹⁾.

Bilharzial polyps are not common in the bladder ⁽¹⁹⁾. Repeated egg deposition in small numbers leads to mucosal elevation with hyperplasia and *polyp* formation. Grossly, it may be single or multiple, sessile, pedunculated or complex. Microscopically, it shows connective tissue core and cellular granuloma around the ova ⁽⁴⁾.

Bilharzial ulcers develop in 20% of bilharzial bladders on the superior and posterior walls ⁽¹⁹⁾. The ulcer is formed by numerous causes. Mucosal damage by penetrating ova leads to mucosal shedding. Shedding of atrophic mucosa of sandy patches may participate. Ulceration of polyp ⁽⁴⁾ may also be the cause.

All of these previous lesions lead to **painless terminal hematuria** ⁽²¹⁾.



Epithelial changes like *hyperplasia*, *Brunn's nests*, *cystitis cystica*, *cystitis glandularis* and *squamous metaplasia* may occur in the transitional epithelium of the bladder ⁽¹⁹⁾. Some of these lesions are premalignant. Squamous cell carcinoma that may result may also cause *hematuria*. This will be discussed later.

Clinical Findings

Urinary frequency and dysuria are early symptoms of *S. haematobium*, but **intermittent terminal hematuria** is the classic presenting feature ⁽²³⁾. Suprapubic or perianal pain may occur intermittently with bladder distention. Hydronephrosis from granulomas in the bladder wall, ureters and urethra is common ⁽²³⁾.

URINARY STONES AND HEMATURIA

Urolithiasis, also called *nephrolithiasis*, is the process of forming a stone in the kidney (or lower down in the urinary tract). The stones themselves are called *renal calculi* ⁽³⁹⁾. Stones may form at any level in the urinary tract, but most arise in the kidney ⁽¹³⁾.

Types of stones:

There are four main types of calculi ⁽¹³⁾. These types can be classified into *primary (metabolic) stones*, for which urinary infection is not essential for their formation and *secondary (infected) stones* ⁽⁵⁾.



Primary (Metabolic) Stones:

- a) **Calcium Stones:** composed largely of *calcium oxalate* or calcium oxalate mixed with *calcium phosphate* ⁽¹³⁾. These stones are usually multiple, hard with *spiny* surface. This leads to injury of urinary mucosa and hemorrhage which leads to dark staining of the stones ⁽⁵⁾

Figure 3**Calcium Oxalate Stone**

Surface is rough; color brown, probably due to old blood pigment ⁽¹⁵⁾

- b) **Uric Acid and Urate Stones** ⁽⁵⁾: It is usually single, hard with a smooth surface and yellowish brown color ⁽⁵⁾. In contrast to the radiopaque calcium stones, uric acid stones are *radiolucent* ⁽¹³⁾.

Figure 4**Uric Acid and Urates Stone**

Smooth and light brown in color ⁽¹⁵⁾

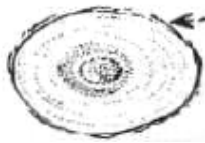
- c) **Cystine Stones** ⁽⁵⁾: made up of cystine ⁽¹³⁾. Soft and yellowish green ⁽⁵⁾. *Cystine stones* are caused by genetic defects in the renal reabsorption of amino acids, including cystine, leading to cystinuria ⁽¹³⁾.



Secondary (Infected) Stones:

Triple Phosphate Stone ⁽⁵⁾ or *struvite stones*, composed of magnesium ammonium phosphate ⁽¹³⁾. It is usually single, large white and friable with a smooth surface ⁽⁵⁾. These stones are formed largely after infections by bacteria (e.g. *Proteus* and some staphylococci) that convert urea to ammonia. The resultant alkaline urine causes the precipitation of magnesium ammonium phosphate salts ⁽¹³⁾.

Figure 5



Phosphate Stone

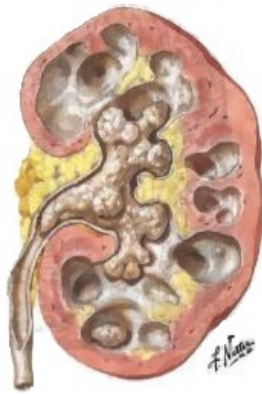
Flaking surface; greyish white ⁽¹⁵⁾

It is to be noted that commonly the stones are mixed. For example, urate stones frequently have a rough covering of oxalate. Both oxalate and urate stones tend to develop a covering of phosphates ⁽¹⁵⁾.

Morphology of Stones

Stones are unilateral in about 80% of patients. The favored sites for their formation are within the renal calyces and pelves and in the bladder ⁽¹³⁾. Often, many stones are found in one kidney. They tend to be small (average diameter 2-3 mm) and may be smooth or jagged. Occasionally, progressive accretion of salts leads to the development of branching structures known as ***staghorn calculi***. These massive stones are usually composed of magnesium ammonium phosphate ⁽¹²⁾. Plain radiographs of the abdomen may detect the stone ⁽³⁷⁾.



Figure 6**Staghorn calculus**

This large single stone is associated with suppuration and ulceration of the pelvis and calyces. It is composed mainly of phosphates⁽¹⁵⁾.

Figure 7

Intravenous pyelogram showing left hydronephrosis resulting from a stone at the ureterovesical junction⁽³⁶⁾

Figure 8

Plain abdominal radiograph showing radiopaque stones of both kidneys (arrows) consistent with a stag horn calculi⁽³⁶⁾.

Aetiology

The cause of stone formation is often obscure, particularly in the case of calcium-containing stones. Probably involved is a confluence of predisposing conditions⁽¹²⁾. The following are modern theories explaining urolithiasis.

Pathogenesis

Urinary tract stone is likely caused by one of two basic phenomena. **The first phenomenon** is *supersaturation* of the urine by stone-forming constituents, including calcium, oxalate, and uric acid⁽³⁵⁾. *Supersaturation* here means increased urine concentration of the stone's constituents, so that it exceeds their solubility in urine⁽¹²⁾. Crystals or foreign bodies can act as *nidi*, upon which ions from the supersaturated urine form microscopic crystalline structures. This is likely the underlying cause of uric and cystine stones. **The second phenomenon**, which is most likely responsible for calcium oxalate stones, is deposition of stone material on a renal papillary calcium phosphate nidus. Calcium phosphate precipitates in the basement membrane of the thin loops of Henle, erodes into the interstitium, and then accumulates in the subepithelial space of the renal papilla. The subepithelial deposits, which have long been known as *Randall plaques*, eventually erode through the papillary urothelium. Randall plaques are always composed of calcium phosphate⁽³⁵⁾.

Predisposing factors for stone formation

1. **Urinary pH:** Urate and oxalate stones form in acidic urine; phosphate stones form in alkaline urine⁽¹⁵⁾.
2. **Dehydration**⁽¹⁵⁾: causing decreased water content of urine⁽⁵⁾ and increased urinary concentration⁽¹⁵⁾.
3. **Stasis:** Obstruction to urine flow encourages salt precipitation⁽¹⁵⁾.
4. **Renal disease:** The pH of the urine is frequently disturbed, and the composition of the urine is always altered⁽¹⁵⁾.



- a. *Urinary infection* predisposes to precipitation of urinary crystalloids through formation of a nucleus (pus cells, detached necrotic cells) and changing the pH of urine ⁽⁵⁾.
- b. *Renal tumors* encourage stone formation. Areas of tumor necrosis may calcify, and tumors tend to cause urinary stasis.

5. Metabolic Factors:

1. Excess calcium in urine (hypercalcuria) as in hyperparathyroidism ⁽⁵⁾.
 2. Excess uric acid and urates in urine as in cases of gout ⁽⁵⁾.
 3. Excess oxalates (oxaluria) ⁽⁵⁾ due to hereditary metabolic error or excess intake in diet (mango, tomato,....) ⁽¹⁵⁾.
 4. Familial Cystinuria ⁽⁵⁾.
6. **Lack of substances** that normally inhibit mineral precipitation. Inhibitors of crystal formation in urine include *Tamm-Horsfall protein*, *osteopontin*, *pyrophosphate*, *mucopolysaccharides*, *diphosphonates*, and a glycoprotein called *nephrocalcin* ⁽¹²⁾.

Effects and complications

Stones may be present without producing either symptoms or significant renal damage. This is particularly true with *large stones* ⁽¹²⁾. Larger stones cannot enter the ureters and are more likely to remain silent within the renal pelvis ⁽¹³⁾. In general, smaller stones are most hazardous, because they may pass into the ureters ⁽¹³⁾ producing a typical intense pain known as *renal or ureteral colic*. Often at this time there is ***gross hematuria*** ⁽¹²⁾ due to traumatic injury of the urothelium ⁽⁵⁾.



Stones less than 5 mm were less likely to be associated with hematuria. Hematuria associated with flank pain may suggest a diagnosis of nephrolithiasis, especially if the pain is colicky in nature⁽³⁷⁾.

Stones also predispose to *superimposed infection*, both by their obstructive nature and the trauma they produce⁽¹³⁾.

With the development of stasis and infection (on top of an existing stone), *further stone formation* is encouraged. This can lead to peculiar lesions e.g. staghorn calculi⁽¹⁵⁾.

Stones and infection in the pelvis can lead to *squamous metaplasia* of the epithelium. In a few instances, this may develop into squamous carcinoma⁽¹⁵⁾. Squamous cell carcinoma may be associated with **hematuria**. *This will be discussed later.*

GLOMERULONEPHRITIS AND HEMATURIA

Glomerulonephritis (GN) is a renal disease characterized by inflammation of the glomeruli or small blood vessels in the kidney⁽⁴³⁾.

Glomerulonephritis can be classified into *primary glomerulonephritis* which mainly affects the kidney and *secondary glomerulonephritis* in which the kidneys are affected as a part of another disease as SLE, hypertension, diabetes mellitus⁽⁵⁾.

Many types of glomerulonephritis are present. In this research, we will focus on the most common types of glomerulonephritis that are



associated with hematuria. These are *poststreptococcal glomerulonephritis*, *crescentic glomerulonephritis* and *membranoproliferative glomerulonephritis*.

Acute Post Streptococcal Glomerulonephritis

Aetiology

This is an immune complex disease. It starts as an upper respiratory infection with nephritogenic strains of *group A beta hemolytic streptococci*. Antibodies are formed and combine with streptococcal antigens leading to the formation of immune complexes. These immune complexes are deposited on the basement membrane of glomerular capillaries⁽⁵⁾.

Once Immune complexes are deposited, they *activate* the complement leading to release of biologically active substances which increase the vascular permeability and *recruit* neutrophils and monocytes triggering inflammation. Attempted phagocytosis of immune complex or the fixed antigen by the phagocytic cells leads to secretion of additional proinflammatory substances as well as lysosomal enzymes capable of digesting glomerular basement membrane and reactive oxygen species that damage the capillary. Aggregated platelets cause microthrombi leading to local ischemia that further damage the tissue. All these mechanisms allow necrosis of the glomerular capillaries, escaping of the RBCs into the urine causing **hematuria**⁽¹²⁾.



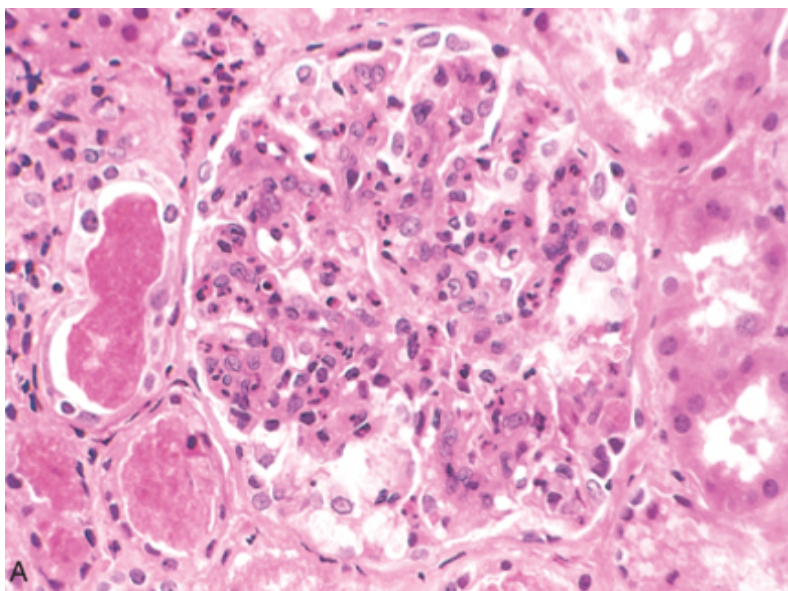
Pathological Picture ⁽⁵⁾

Grossly, there is mild bilateral kidney enlargement. Cortical oedema and petechial hemorrhages may be seen.

Microscopically, Glomeruli are enlarged and show proliferation of epithelial, endothelial and mesangial cells. Several neutrophils are found in the glomerular capillaries. Bowman's capsular space shows neutrophils, erythrocytes and some albumin. Renal Tubules show cloudy swelling and casts (mainly blood casts). The interstitium of the kidney shows oedema and neutrophils.

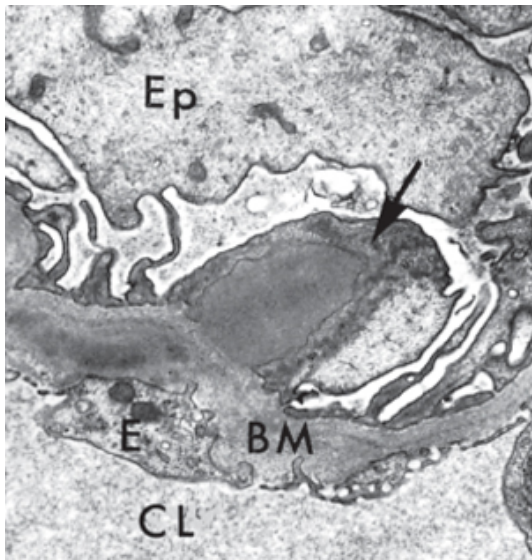
By the **electron microscope**, "Humpy-lumpy" immune complex deposits are seen between podocytes and basement membranes. **Immunofluorescence** reveals that the deposits consist of IgG, IgM and complement.

Figure 9



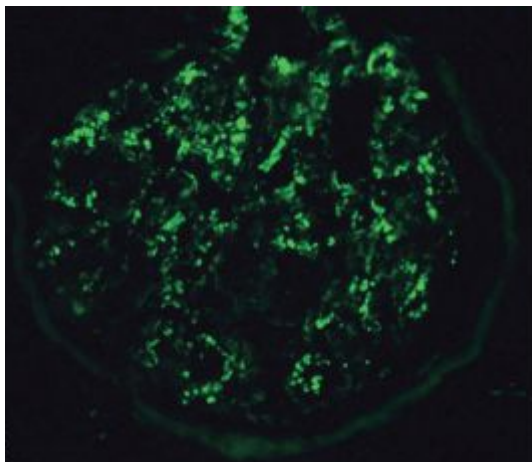
Poststreptococcal GN

Glomerular hypercellularity is caused by intracapillary leukocytes and proliferation of intrinsic glomerular cells. Note the red cell casts in the tubules ⁽¹²⁾

Figure 10**Poststreptococcal GN (EM)**

Typical electron-dense subepithelial "hump" (arrow) and intramembranous deposits.

BM, basement membrane; CL, capillary lumen; E, endothelial cell; Ep, visceral epithelial cells (podocytes).

Figure 11**Poststreptococcal GN****(Immunofluorescent stain)**

demonstrates discrete, coarsely granular deposits of complement protein C3, corresponding to "humps" in previous figure

Clinical Picture

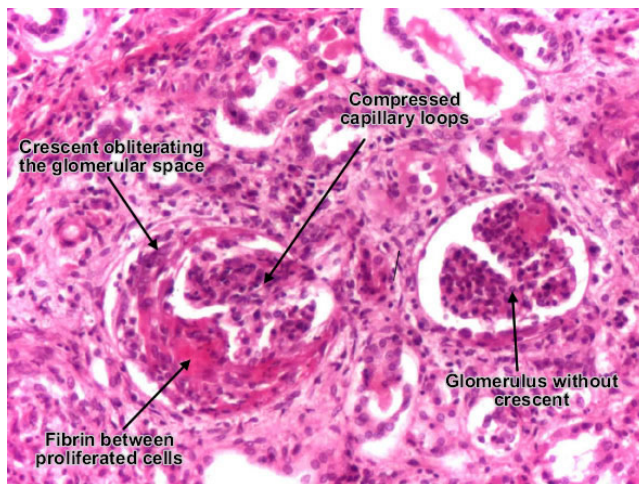
The disease typically presents with hematuria associated with edema, hypertension, or both ⁽¹⁶⁾. This is usually associated with mild proteinuria and oliguria ⁽⁵⁾ and are collectively referred to as the *nephritic syndrome*. Urine appears dark (Cola like) and its specific gravity is high ⁽⁵⁾. The subclinical form of the disease can present with microscopic hematuria with or without hypertension ⁽¹⁶⁾.



Rapidly Progressive Glomerulonephritis (RPGN) (Crescentic Glomerulonephritis)

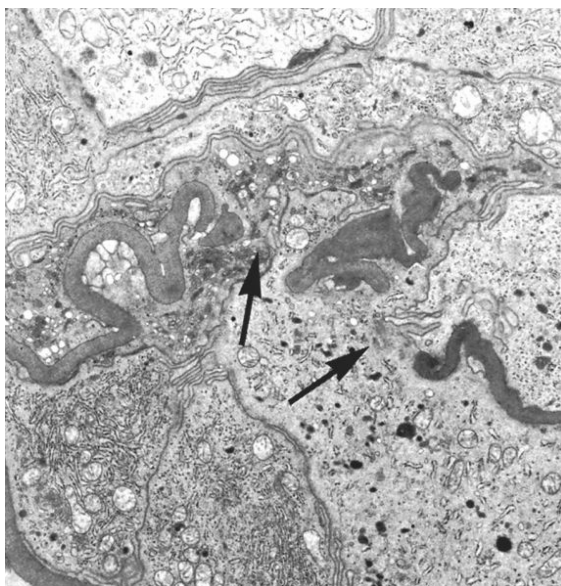
RPGN is a clinical syndrome and not a specific etiological form of GN. Regardless of the cause, the histological picture is characterized by the presence of **crescents**. Clinically it is characterized by massive hematuria, severe oliguria or anuria and variable proteinuria ⁽¹²⁾.

Figure 12



Crescentic glomerulonephritis

Figure 13



Crescentic glomerulonephritis.
Electron micrograph showing characteristic wrinkling of GBM with focal disruptions (arrows) ⁽¹³⁾



RPGN may be *immune mediated*, as when autoantibodies develop to the glomerular basement membrane (GBM) in anti-GBM antibody disease or when it develops consequent to immune complex deposition. It can also be *pauci-immune*, associated with antineutrophil cytoplasmic antibodies. On basis of immunologic findings, RPGN is classified into three types⁽¹²⁾.

Anti-GBM antibody type

In this type of glomerular injury, antibodies are directed against **fixed antigen** on GBM. Antibodies bound to cellular or tissue antigens (GBM) activate the complement system triggering inflammation.

Pathologic picture:

Glomeruli show segmental necrosis and GBM breaks⁽¹²⁾. Proliferation of endothelial cells and mesangial cells and parietal cells is observed⁽²⁰⁾. There is leukocytic infiltration and the glomerular capillaries undergo necrosis and hemorrhage⁽¹²⁾.

Immune complex mediated type

Whatever the antigen may be, endogenous or exogenous, antigen-antibody complexes are formed and are then trapped in the glomeruli, where they produce injury⁽¹²⁾.

Pathologic picture:

There is segmental necrosis as described in Anti-GBM antibody GN, however, in contrast there is *granular deposition* of the



immunocomplexes and the segments without necrosis show evidence of the underlying immune complex GN ⁽¹²⁾.

Pauci – immune type

This type is characterized by the lack of anti-GBM antibodies or significant immune complex deposition detected by electron microscopy and Immunofluorescence ⁽¹²⁾.

Pathologic picture:

Glomeruli show segmental necrosis as described with Anti-GBM antibody GN, however, in contrast, no significant deposits can be detected by electron microscopy and no immunoglobulin or complement by Immunofluorescence or nearly so ⁽¹²⁾.

Membranoproliferative Glomerulonephritis (MPGN)

In this type, there is *thickening* of the glomerular capillary wall, which appears double “*tram track appearance*” due to leukocytic infiltration ⁽¹⁾, and *increase* in the number of cells in the glomerular tuft ⁽¹¹⁾.

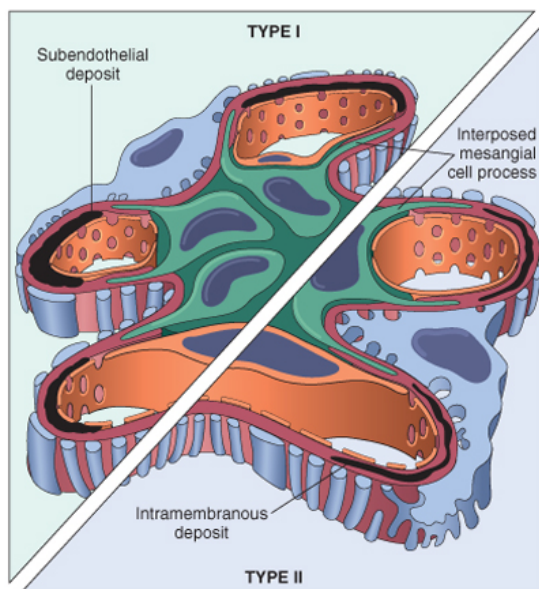
Clinically, MPGN patient presents with ***nephritic syndrome*** (hematuria, oliguria, mild proteinuria, hypertension and nephritic edema), ***nephrotic syndrome*** (massive proteinuria, hypoalbuminemia, severe generalized edema, hyperlipidemia, lipiduria) or both ⁽⁵⁾. Two major types of MPGN are recognized on the basis of distinct



ultrastructural, immunofluorescence microscopic, and pathogenic findings.

In **MPGN type 1**, there is subendothelial deposits of IgG, IgM and complement ⁽⁵⁾. **MPGN type 2** is also known as “dense deposit disease” ⁽¹⁾, as the glomerular basement membrane shows dense deposits of complement ⁽⁵⁾.

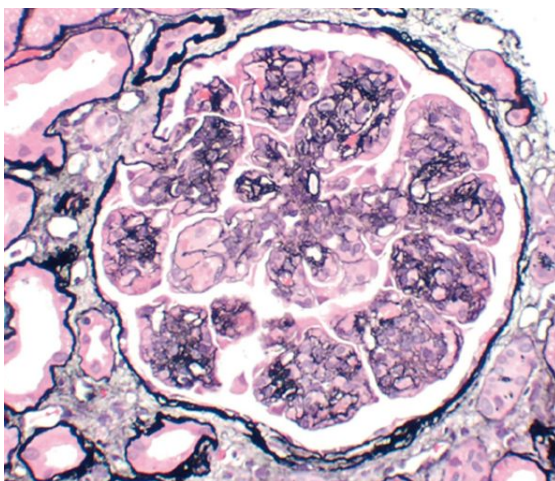
Figure 14



Schematic representation of patterns in the two types of membranoproliferative GN.

In type I there are subendothelial deposits; type II is characterized by intramembranous dense deposits (dense-deposit disease). In both, mesangial interposition gives the appearance of split basement membranes when viewed by light microscopy ⁽¹²⁾

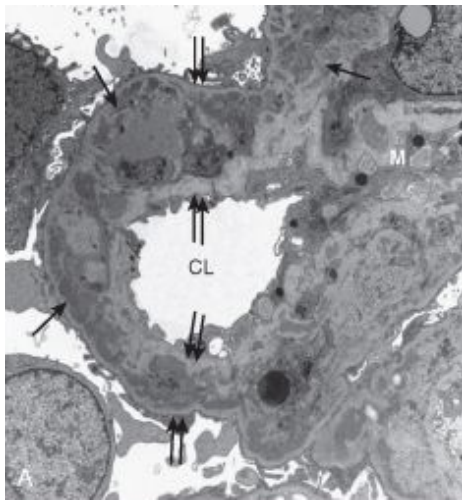
Figure 15



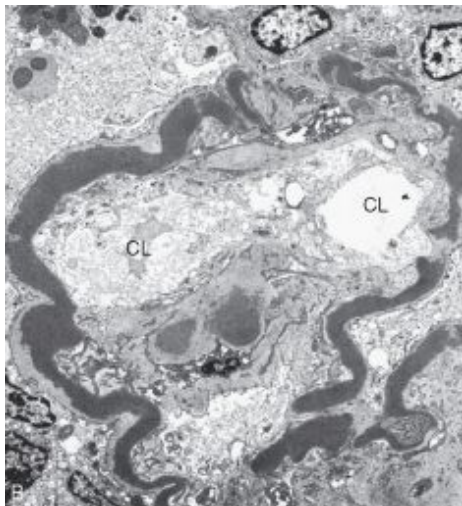
Membranoproliferative

glomerulonephritis, showing mesangial cell proliferation, increased mesangial matrix (staining black with silver stain), basement membrane thickening with segmental splitting, accentuation of lobular architecture, swelling of cells lining peripheral capillaries, and influx of leukocytes (endocapillary proliferation) ⁽¹³⁾



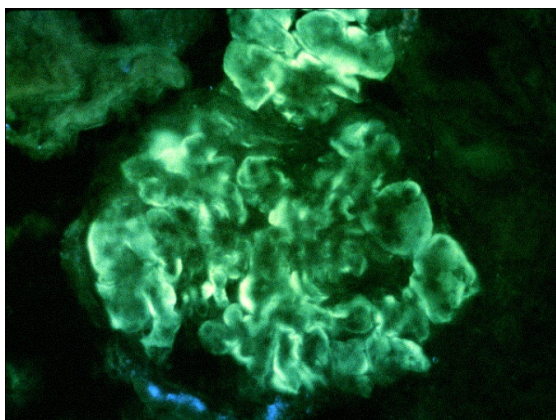
Figure 16

Membranoproliferative glomerulonephritis, type I. Note discrete electron-dense deposits (*arrows*) incorporated into the glomerular capillary wall between duplicated (split) basement membranes (*double arrows*), and in mesangial regions (M); CL, capillary lumen

Figure 17

Dense-deposit disease (type II membranoproliferative GN)

There are markedly dense homogeneous deposits within the basement membrane proper. CL, capillary lumen. In both, mesangial interposition gives the appearance of split basement membranes when viewed in the light microscope

Figure 18

MBGN 1 (Immunofluorescence)

TUMORS AND HEMATURIA

Macroscopic hematuria has a risk of 20–25% of cancer (bladder, renal, and prostatic) and the risk of detecting similar cancers in patients with microscopic hematuria is around 4% ⁽⁷⁾.

In this research, we will focus on the most frequent tumors of the genitourinary system that cause hematuria. Tumors are divided according to the anatomical site into *tumors of the kidneys, tumors of the bladder, tumors of the prostate and other tumors of the renal pelvis and ureter*.

Tumors of the Kidneys

Tumors of the kidneys are one of the causes of upper urinary tract *hematuria*. The most common cancer of the kidney is renal *cell carcinoma*. *Transitional cell carcinoma* is a less common type of cancer involving the kidneys or ureters ⁽⁴¹⁾. Yet most small kidney tumors do not cause any bleeding, and in recent years, a growing number of kidney cancers have been diagnosed in patients without any urinary symptoms who undergo abdominal X-rays for other unrelated reasons ⁽⁴¹⁾.

Less common causes of upper urinary tract hematuria include *benign tumors*, such as angiomyolipoma or oncocytoma ⁽⁴¹⁾.

Features of Hematuria in Kidney Tumors

Hematuria is the most common symptom of kidney cancer. About half of those diagnosed with kidney cancer will have this symptom when



they first go to the doctor ⁽⁴⁰⁾.

1- The blood does *not have to be there all the time*. It can come and go ⁽⁴⁰⁾. Therefore, both the doctor and the patient may get the impression that the problem has gone away. This can mean that an early, treatable cancer in the kidney or bladder is allowed to grow to the stage where it may not be so easy to treat ⁽⁴⁰⁾.

2- Sometimes, the blood *cannot be seen by the naked eye* but can be picked up by a simple urine test ⁽⁴⁰⁾.

3- Special microscopic examination of the urine often shows the malignant or *cancerous cells* ⁽⁴¹⁾.

Pathology of the Most Frequent Kidney Tumors

In this research, we will focus on *renal cell carcinoma*, the most frequent tumor of the kidney. Renal cell carcinoma represents on average over 90% of all malignancies of the kidney that occur in adults in both sexes ⁽¹⁸⁾.

Renal cell carcinoma

Renal cell cancer is the seventh leading malignant condition among men and the twelfth among women, accounting for 2.6% of all cancers ⁽¹⁸⁾. The classic symptomatic presentation of renal cell carcinoma includes the triad *hematuria, flank pain, and palpable abdominal mass*.

Morphology

Renal cell carcinomas may arise in any portion of the kidney, but



more commonly affects the poles. One of the striking characteristics of renal cell carcinoma is its tendency to invade the renal vein (Figure 9) and grow as a solid column of cells within this vessel. Further growth may produce a continuous cord of tumor in the inferior vena cava that may extend into the right side of the heart⁽¹³⁾.

Different types of renal cell carcinoma are present. The three most common forms are *clear cell carcinoma*, *papillary carcinoma* and *chromophobe renal carcinoma*.

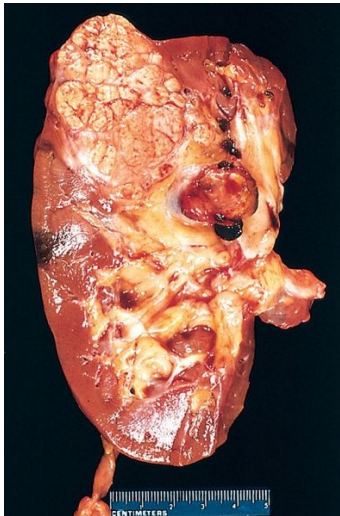
Clear cell carcinoma⁽¹³⁾

This is the most common type, accounting for 70% to 80% of renal cell cancers. The tumors are made up of cells with clear or granular cytoplasm and are nonpapillary.

Clear cell carcinomas arise most likely from proximal tubular epithelium, and usually occur as solitary unilateral lesions.

Grossly, They are spherical masses, which can vary in size, composed of bright yellow-gray-white tissue that distorts the renal outline. There are commonly large areas of ischemic, opaque, gray-white necrosis, and foci of hemorrhagic discoloration. The margins are usually sharply defined and confined within the renal capsule (Figure 9).

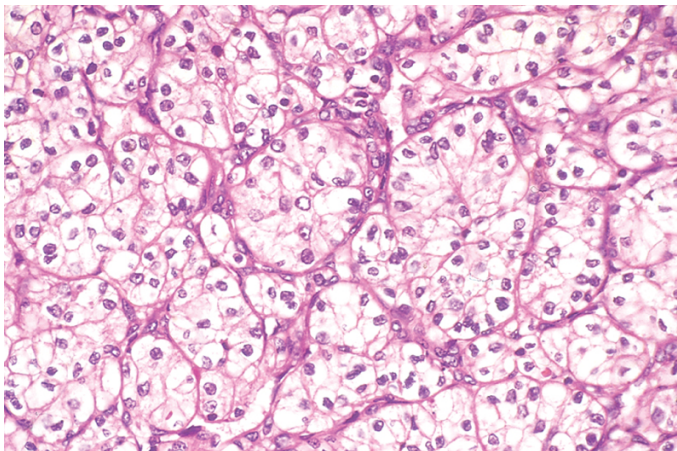


Figure 19**Renal cell carcinoma.**

Typical cross-section of yellowish, spherical neoplasm in one pole of the kidney.

Note the tumor in the dilated thrombosed renal vein. ⁽¹³⁾

Microscopically, the growth pattern varies from solid to trabecular (cordlike) or tubular (resembling tubules). The tumor cells have a rounded or polygonal shape and abundant clear or granular cytoplasm, which contains glycogen and lipids (Figure 10). The tumors have delicate branching vasculature and may show cystic as well as solid areas. Most tumors are well differentiated, but some show marked nuclear atypia with formation of bizarre nuclei and giant cells.

Figure 20

High-power detail of the clear cell pattern of **renal cell carcinoma** ⁽¹²⁾



Papillary carcinoma⁽¹³⁾

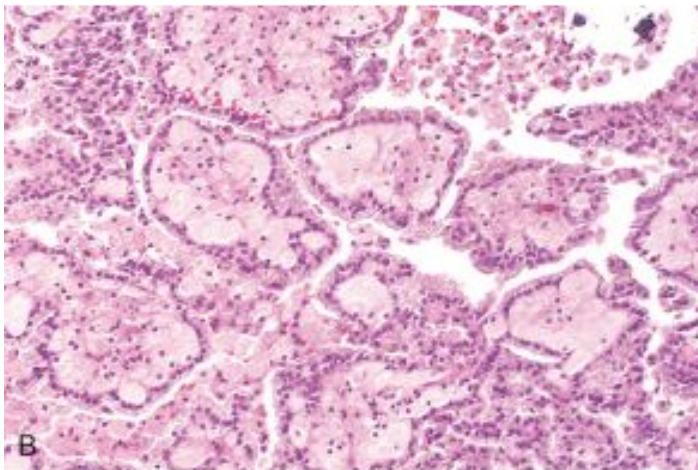
This type accounts for 10% to 15% of renal cancers. It is characterized by a papillary growth pattern.

Papillary tumors, thought to arise from distal convoluted tubules, can be multifocal and bilateral.

Grossly they are characterized by a spherical boundary and a beige to white color. They can exhibit central necrosis resulting from a poor vascular supply and frequent hemorrhages. In some cases this feature can be so extensive as to mimic a cyst both radiologically and grossly⁽¹⁸⁾.

Microscopically they are composed of cuboidal or low columnar cells arranged in papillary formations. Interstitial foam cells are common in the papillary cores (Figure 11). The stroma is usually scanty but highly vascularized.

Figure 21



Papillary type.
Note the papillae and foamy macrophages in the stalk⁽¹³⁾

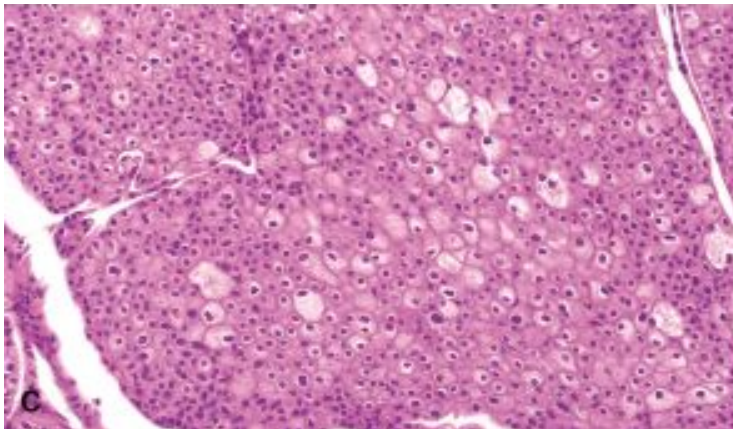


Chromophobe renal carcinoma⁽¹³⁾

This type represents 5% of renal cell cancers. They are thought to grow from intercalated cells of collecting ducts and have an excellent prognosis compared with that of the clear cell and papillary cancers.

Microscopically it is made up of pale eosinophilic cells with prominent cell membranes, often with a perinuclear halo, arranged in solid sheets with a concentration of the largest cells around blood vessels (Figure 12).

Figure 22



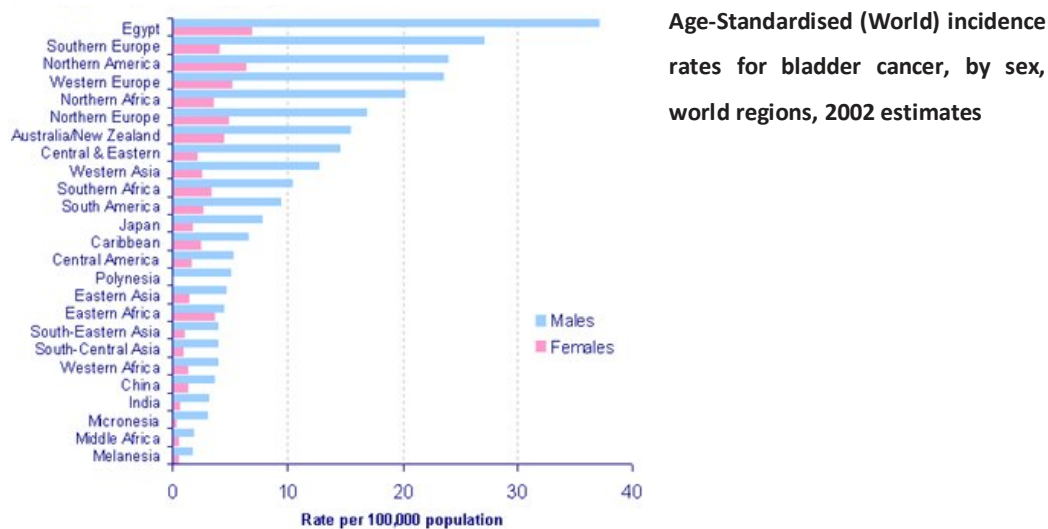
Chromophobe type⁽¹³⁾

Tumors of the Bladder

Bladder cancer is the second most common GU cancer with 54,300 new cases annually and 12,100 deaths from the disease⁽²²⁾. Egypt has the highest reported rate (37 per 100000 populations) in the world due to endemic schistosomiasis⁽⁴²⁾. (Figure 13)



Figure 23



Approximately three-quarters of patients with bladder cancer present with **painless intermittent hematuria**. It is estimated that approximately 20% of patients being evaluated for gross hematuria will subsequently be diagnosed with bladder cancer. Similarly, of patients presenting with microscopic hematuria, up to 10% will be diagnosed with bladder cancer ⁽¹⁸⁾.

One-quarter of patients with bladder cancer will present with irritative voiding symptoms of urgency, frequency, and dysuria, symptoms frequently misinterpreted as signs of a urinary tract infection but that may signify either trigone involvement with tumor or the presence of carcinoma in situ ⁽¹⁸⁾. Primary carcinoma in situ rarely presents with hematuria ⁽⁷⁾.

Features of Hematuria in Bladder Tumors

1- Hematuria -the cardinal sign of bladder cancer- is classically painless and commonly is intermittent ⁽⁷⁾.

2- Investigation of microscopic hematuria in patients with bladder cancer is controversial ⁽⁷⁾ and tends to be unpredictable and inconsistent; therefore, a single negative urinalysis does not exclude the possibility of cancer ⁽¹⁸⁾. Currently the recommendation is that persistent evidence of hematuria on microscopy or dipstick testing in patients older than 40 years should be referred for investigation ⁽⁷⁾.

3- Bladder cancer can often cause hematuria with no other symptoms ⁽⁴¹⁾ or it may present with irritative symptoms ⁽⁷⁾

Pathology of Bladder Cancer ⁽⁴²⁾

In developed countries, around 90% of bladder cancers are *transitional cell carcinomas* while the remaining 10% are *squamous cell carcinomas* and *adenocarcinomas*. Benign transitional cell papillomas have sometimes and in some places been registered as invasive carcinomas.

Where the bladder cancer is associated with chronic bladder infection, most commonly with schistosomiasis, the usual histology is *squamous cell carcinoma*. Schistosomiasis-associated bladder cancer has an earlier mean age at onset and tends to present at a later stage than transitional cell carcinomas.

In countries where schistosomiasis is endemic, such as Egypt, bladder cancer is the most common cancer in men.



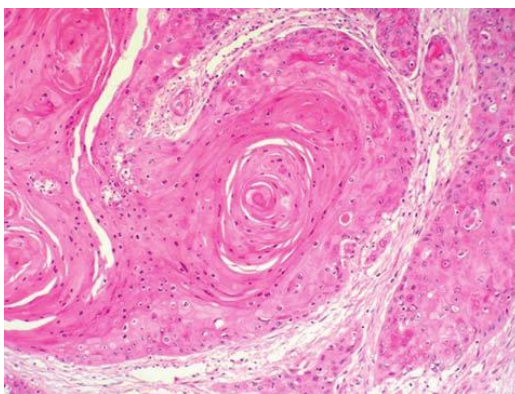
Squamous cell carcinoma⁽¹⁸⁾

A malignant neoplasm derived from the urothelium showing histologically pure squamous cell phenotype. Schistosomiasis and chronic urinary tract infection are conditions associated with the development of squamous cell carcinoma. The presence of keratinizing squamous metaplasia in the adjacent flat epithelium, especially if associated with dysplasia, supports a diagnosis of squamous cell carcinoma.

The invasive tumors may be *well differentiated* (Figure 14) with well-defined islands of squamous cells with keratinization, prominent intercellular bridges, and minimal nuclear pleomorphism. They may also be *poorly differentiated*, with marked nuclear pleomorphism and only focal evidence of squamous differentiation.

The verrucous form of squamous cell carcinoma is an uncommon variant that occurs most frequently in patients with schistosomiasis. Patients undergoing radical surgery appear to have an improved survival as compared to radiation therapy and/or chemotherapy.

Figure 24



Well differentiated squamous cell carcinoma with well-defined islands of squamous cells with keratinization (cell nests)



Transitional cell carcinoma⁽¹⁹⁾

This is malignant tumor of transitional epithelium. The tumor may arise de novo or on top of a villous papilloma.

Gross Picture: Commonly the tumor appears as a papillary soft growth with infiltrating base. Non-papillary tumors are ulcerating, fungating or infiltrating.

Microscopic Picture: Sheets of large pale malignant transitional cells with indefinite outlines separated by fibrous stroma.

Prostate tumors

Blood in the urine may also be noted in men who have benign prostatic hyperplasia (BPH) and in some men who have prostate cancer⁽⁴¹⁾.

Tumors of the Renal Pelvis and Ureters⁽¹⁸⁾

Tumors arising in the renal pelvis, the ureter, and the urethra are morphologically similar to those in the bladder.

Tumors of the ureter and renal pelvis account for 8% of all urinary tract neoplasms and are more common in older patients (mean 70 years). More than 90% are urothelial carcinomas. Hematuria and flank pain are the chief presenting symptoms.



OTHER CAUSES OF HEMATURIA

Drug-Induce Hematuria

Many drugs can cause either hematuria or discoloration of urine. Heavy or surreptitious use of analgesics may be associated with analgesic nephropathy, which can be associated with hematuria. Use of oral contraceptives has been associated with loin-pain hematuria syndrome ⁽¹⁶⁾. Drugs as anticoagulants ⁽⁵⁾ and Penicillin (extended-spectrum) ⁽²⁷⁾ have been proved to cause hematuria.

Tuberculosis and Hematuria

Renal tuberculosis can present with gross hematuria, flank pain, dysuria and pyuria. This condition is a local manifestation of a generalized infection and occurs as a result of bloodstream dissemination ⁽¹⁶⁾.

Tuberculosis of the bladder can cause bladder lesions ⁽¹⁶⁾ and may be complicated as *hematuria*.

Figure 25



Renal tuberculosis

In the lower third of the kidney there is a caseous inflammatory mass extending through the whole thickness of the renal cortex. This patient presented with the classic symptom of painless Hematuria. Investigations confirmed the diagnosis of tuberculosis, and nephrectomy was performed ⁽²⁾



Loin-Pain Hematuria Syndrome

Loin-pain hematuria syndrome is rare. The cause is not known⁽¹⁶⁾. This syndrome is frequently, but not exclusively, found in young women receiving estrogen-containing birth control medication⁽¹⁰⁾. It presents with recurrent bouts of gross or microscopic hematuria with or without dysuria but almost always with unilateral or bilateral loin pain. Treatment, in general, is not very satisfactory, but discontinuance of oral contraceptives may result in some relief of loin pain and disappearance of hematuria⁽¹⁰⁾.

Marathon Runners' Hematuria

This form of gross hematuria occurs after prolonged running (usually > 15 km/week) predominantly but not exclusively in males. The hematuria may be associated with the passage of clots and suprapubic and perianal discomfort but usually not with loin pain. It may develop repetitively, but usually disappears quickly upon resting. No treatment is required other than reassurance and reduction of running intensity⁽¹⁰⁾.

Hereditary Causes of Hematuria

Some hereditary causes are associated with hematuria. The most common of which are *thin basement membrane disease* (benign familial hematuria), *Alport syndrome* and *Nail-patella syndrome*. Polycystic Kidney disease is also a congenital disorder that is associated with hematuria. Here we will give some notes on the first two.



Thin basement membrane disease (Benign Familial Hematuria)

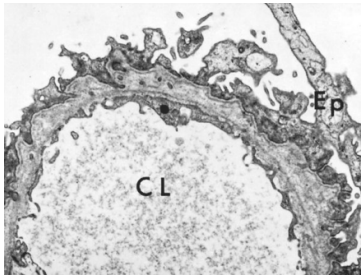
This is a common hereditary lesion ⁽¹³⁾ presents most commonly with microscopic *hematuria*, usually with minimal or no proteinuria. No histologic abnormality is found on ***light*** and ***immunofluorescence microscopy***. Diffuse and uniform thinning of the glomerular basement membrane is seen on ***electron microscopy*** ⁽¹⁶⁾. The anomaly in thin basement membrane lesion has also been traced to mutations in genes encoding α_3 or α_4 chains of type IV collagen. Renal function is normal and prognosis of the disease is excellent ⁽¹³⁾.

Alport syndrome

Alport syndrome is one of the best studied hereditary glomerulopathies. Two forms of Alport syndrome have been recognized on a molecular genetic basis: an *X-linked dominant form* and an *autosomal-recessive form* ⁽¹⁶⁾. The disease manifestations are due to abnormal α_3 , α_4 , or α_5 chain of type IV collagen ⁽¹³⁾. This is due to a mutation in a gene encoding for a protein of type IV collagen ⁽¹⁶⁾. In all cases, the result is defective assembly of type IV collagen, which is crucial for function of the GBM, the lens of the eye, and the cochlea ⁽¹³⁾.

The pathologic findings on ***light microscopy*** are nonspecific. ***Immunofluorescence microscopy*** may show nonspecific granular deposits of C3 and IgM. The salient diagnostic abnormality is the variable thickening, thinning, and lamellation of the glomerular basement membrane seen on ***electron microscopy***.



Figure 26**Alport syndrome**

Electron micrograph of glomerulus with irregular thickening of the basement membrane, lamination of the lamina densa, and foci of rarefaction. Such changes may be present in other diseases but are most pronounced and widespread in hereditary nephritis.

CL, capillary lumen; Ep, epithelium ⁽¹³⁾.

The most common presenting sign is gross or microscopic hematuria, frequently accompanied by red cell casts ⁽¹³⁾. Hematuria may reflect fragility of the glomerular basement membrane in the absence of the normal collagen network formed by the type IV collagen chains ⁽¹⁶⁾. Proteinuria may develop later, and rarely, the nephrotic syndrome develops ⁽¹³⁾. Sensorineural hearing loss, eye defects, and cataracts are commonly associated with this syndrome ⁽¹⁶⁾.

DIFFERENTIAL DIAGNOSIS OF HEMATURIA ⁽¹⁴⁾⁽¹⁷⁾⁽²⁶⁾

Hematuria can be *glomerular* (because of glomerular disease, sometimes called *medical*); or *non-glomerular* (sometimes called *surgical*). Glomerular hematuria can be differentiated from non glomerular hematuria by:

1. The shape of RBCs in urine is *dysmorphic* in cases with glomerular hematuria while it will be normal in case of non-glomerular hematuria.
2. The size of RBCs whose mean corpuscular volume in urine of patient with glomerular hematuria which is *smaller* than it is in peripheral blood but in non glomerular cases it is equal.



3. *Proteinuria* is present in most cases of glomerular hematuria but not in cases of non-glomerular hematuria.
4. *Blood clots* indicate non-glomerular bleeding and can be associated with pain and colic.

Gross hematuria in adults is considered a sign of malignancy until proved other diagnosis. The character of the hematuria may provide a clue to the site of origin. *Initial hematuria*, the presence of blood at the beginning of the urinary stream that clears during the stream, implies an anterior (penile) urethral source. *Terminal hematuria*, the presence of blood at the end of the urinary stream, implies a bladder neck or prostatic urethral source. *Total hematuria*, the presence of blood throughout the urinary stream, implies a bladder or upper tract source. *A vermiform clot* suggests a source arising from the upper urinary tract.

Hematuria and Symptoms

Hematuria with renal colic suggests an *uretral stone*, but the passage of blood clots from a bleeding tumor mimics this scenario. Irritative voiding symptoms in a young woman may suggest *acute bacterial infection* and associated hemorrhagic cystitis, yet the same picture in an older woman or in any male raises concerns about neoplasm. In any situation, if cultures are negative or hematuria persists after therapy, further evaluation is warranted. In the absence of other symptoms, gross hematuria may be more indicative of tumor, but staghorn calculi, glomerulonephropathies, and polycystic kidney disease are also suggested.



Figure 27: Hematuria common causes and associated findings ⁽⁴⁴⁾

SIGNS & SYMPTOMS		MAJOR ASSOCIATED SIGNS AND SYMPTOMS																												
		Abdominal distention	Abdominal pain	Anuria	Bladder distention	Blood pressure, increased	Bowel sounds, hypoactive	Costovertebral angle tenderness	Dysuria	Edema, generalized	Edema of the legs	Fever	Flank mass	Flank pain	Lumbar pain	Murmurs	Nausea	Nocturia	Oliguria	Perineal pain	Polyarthralgia	Polyuria	Proteinuria	Purpura	Rash	Urethral discharge	Urinary frequency	Urinary hesitancy	Urinary urgency	Vomiting
COMMON CAUSES																														
Bladder cancer																														
Bladder trauma																														
Calculi (bladder)																														
Calculi (renal)																														
Coagulation disorders																														
Cervical necrosis (acute)																														
Cystitis (bacterial)																														
Cystitis (chronic interstitial)																														
Cystitis (tubercular)																														
Cystitis (viral)																														
Diverticulitis																														
Glomerulonephritis (acute)																														
Glomerulonephritis (chronic)																														
Nephritis (acute interstitial)																														
Nephritis (chronic interstitial)																														
Nephropathy (obstructive)																														
Polycystic kidney disease																														
Prostatitis (acute)																														
Prostatitis (chronic)																														
Pyelonephritis (acute)																														
Renal cancer																														

(continued)

Investigations of a case of hematuria

1. First exclude hemoglobinuria and myoglobinuria since both of them can also cause positive dipstick test for hematuria. This is done by microscopic examination of fresh urine sample. In case of Hematuria, RBCs could be seen while in the other two conditions no RBCs could be

seen. Also in case of myoglobinuria, clinical examination may show manifestations of muscle disease and the examination of urine by immunoelectrophoresis may show myoglobin. In case of haemoglobinuria, manifestations of haemolysis may be evident.

2. Examination of urine for proteinuria and casts (to diagnose glomerular disease), pus cells and urine culture (for diagnosis of infection), Zheil-Nelsn stain and specific media (for diagnosis of T.B.).

3. Plain X-ray, I.V.P. (if serum creatinine is normal), ultrasound and possibly angiography, for the diagnosis of surgical diseases e.g. stone, malignancy or infection.

4. RBCs in urine could be examined for its shape to differentiate glomerular from non-glomerular causes (by phase contrast microscopy).

5. Kidney function tests.

6. Specific investigations for diagnosis of systemic diseases causing Hematuria e.g. SLE.

7. Kidney biopsy for glomerular Hematuria.

8. Further Invesigations:

- **Imaging:** Further evaluation includes urinary cytology, upper tract imaging, and cystoscopy.
- **Cystoscopy:** can be used to assess for bladder or urethral neoplasm, benign prostatic enlargement, and radiation or chemical cystitis.
- **Follow-up**



COMPLICATIONS OF HEMATURIA

It is rare for patients to experience complications from microscopic hematuria. A patient with recurrent or persistent gross hematuria, however, can easily become *anemic* and such patients may need treatment for this condition as part of their overall management (22).

Hematuria may be heavy enough to *clot* and cause obstruction of the urinary tract with which patients may experience ⁽³⁸⁾ *clot "colic"* similar to the pain felt with passing a ureteral calculus ⁽²²⁾. Difficulty emptying the bladder may occur if a clot obstructs the outflow of the bladder. This may worsen to the point of *urinary retention* ⁽³⁸⁾. The clots may be too large to pass through the urethra. These clots require evacuation through a large Foley catheter or sometimes through a cystoscope under anesthesia, or *bladder rupture* could result ⁽²²⁾.

DURATION OF HEMATURIA

Duration of hematuria depends on its cause. For example, Hematuria related to strenuous exercise usually goes away within 1 or 2 days after the exercise. Hematuria from a urinary tract infection will end when the infection is cured. Other causes might take longer to clear up (31).



TREATMENT OF HEMATURIA

The treatment of hematuria depends on its cause ⁽³¹⁾. If no serious condition is causing the hematuria, no treatment is necessary ⁽³²⁾.



CLINICAL CASES

Case I: Transitional Cell Carcinoma

Personal History:

- Gaber Abd El-Magid Morsy
- 74 years old
- He was born and lives in Menouf.
- He is married with 5 sons.
- He is a smoker, with smoking index 400 (heavy smoker).

Complaint:

- Reddish urine since month.

History of patient's illness:

- The condition started since one month by appearance of blood in urine. The condition was of acute onset and progressive course. It was firstly initial but turned to total hematuria. It was painless then frequency of micturation and nocturia occurred. In addition, there is urgency.
- No dysuria, No percipetancy, No other disorder of uria (average volume, no abnormal content)

System review:

- No other systemic symptoms.

Past history:

- There is a history of schistosomiasis; he received medication for it in the form of tablets.
- No DM, No HTV.
- No history of surgeries.



٢٠١١-٢٠١٢
٢٠١١/١٢/٢٠
الكلية الطبية
٢٠١١/١٢/٢٠

نوع الإقامة

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رقم المستشفى

التاريخ

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رقم التذكرة

إستقبال

عيادة

قسم :

عضو هيئة التدريس والطبيب المعالج :

اسم المريض :

سجل الإقامة :

الجنسية :

عمر المريض :

ذكر / أنثى :

مرسل من :

بإفادة رقم :

ملاحظات طبيب العيادة أو الاستقبال

Bladder Mass, Right lateral wall 3.2 X 2.6 cm.

حالة المريض عند الدخول :

التشخيص المبدئى :

الإمضاء	الإسم	مساء	صباحا
No DM	- No H/o previous operations		
No Htn			
No allergy			
DRE: flat, no induration			

طبيب العيادة أو الإستقبال

حكيمة القسم

الطبيب المقيم بالوحدة

قاعة :

سرير :

اسم :

مرفقات التذكرة :

١ - U/S → NO BP bilaterally.

٢ - → UB mass, Rt. lct. 3.2 X 2.6 cm.

٣ -

٤ -

٥ -

Some Investigations of Case 1


معمل الرصاصات
 للمتحاليل الطبية
 و أبحاث الدم

Name: Date:
 Age: Referral by:

Urine Analysis

Physical examination		(Normal)
Volume	R Sample	R Sample
Colour	Yellow	A. Yellow
Aspect	Semi turbid	Clear
Reaction	Acidic	Acidic
Sp. Gr	1020	1015-1030
Chemical examination		
Albumin	Trace	nil
Sugar	nil	nil
Acetone	nil	nil
Bile Salts	nil	nil
Nitrite	nil	nil
Bilirubin	nil	nil
Urobilinogen	N Trace	n. trace
Microscopic examination		
RBCs	Over 100	(0-4)
WBCs	4-6	(0-4)
Epith. cells	(+)	nil
Casts	nil	nil
Crystals	nil	nil
Amorphous	nil	nil
Oxalate	nil	nil
Others	nil	nil

25/1
 2010

Name:- GABER ABD RABOU.
 Referred from: Prof. Dr.

Date: 26 / 1 / 2010
 AMR EL-ALAIMY.

Pelvi abdominal ultrasonography revealed:

*LIVER :- is of average size showing coarse echopattern, no focal lesions are detected.

Portal vein is of average caliber, no thrombosis is detected.

*BILIARY SYSTEM :- The gall bladder shows normal wall thickness with no stones are detected.

No intra or extra- biliary radicals dilatation are detected.

*SPLEEN :- is of average size it measures about 10 cm in its long axis showing homogenous echopattern, no focal lesions are detected. The splenic vein is within normal with no perisplenic collaterals are detected.

*BOTH KIDNEYS :-

They are of average size with normal cortico-medullary differentiation. No renal stones or back pressure changes are detected. The parenchymal thickness and echogenicity are within normal.

*THE PANCREAS :- is of average size showing normal size and echogenicity.

*NO ENLARGED ABDOMINAL L.Ns ARE DETECTED.

*NO ASCITES IS SEEN.

*URINARY BLADDER :- shows a right lateral wall cauliflower echogenic mass measuring about 3.2 x 2.6cm, no stones are detected.

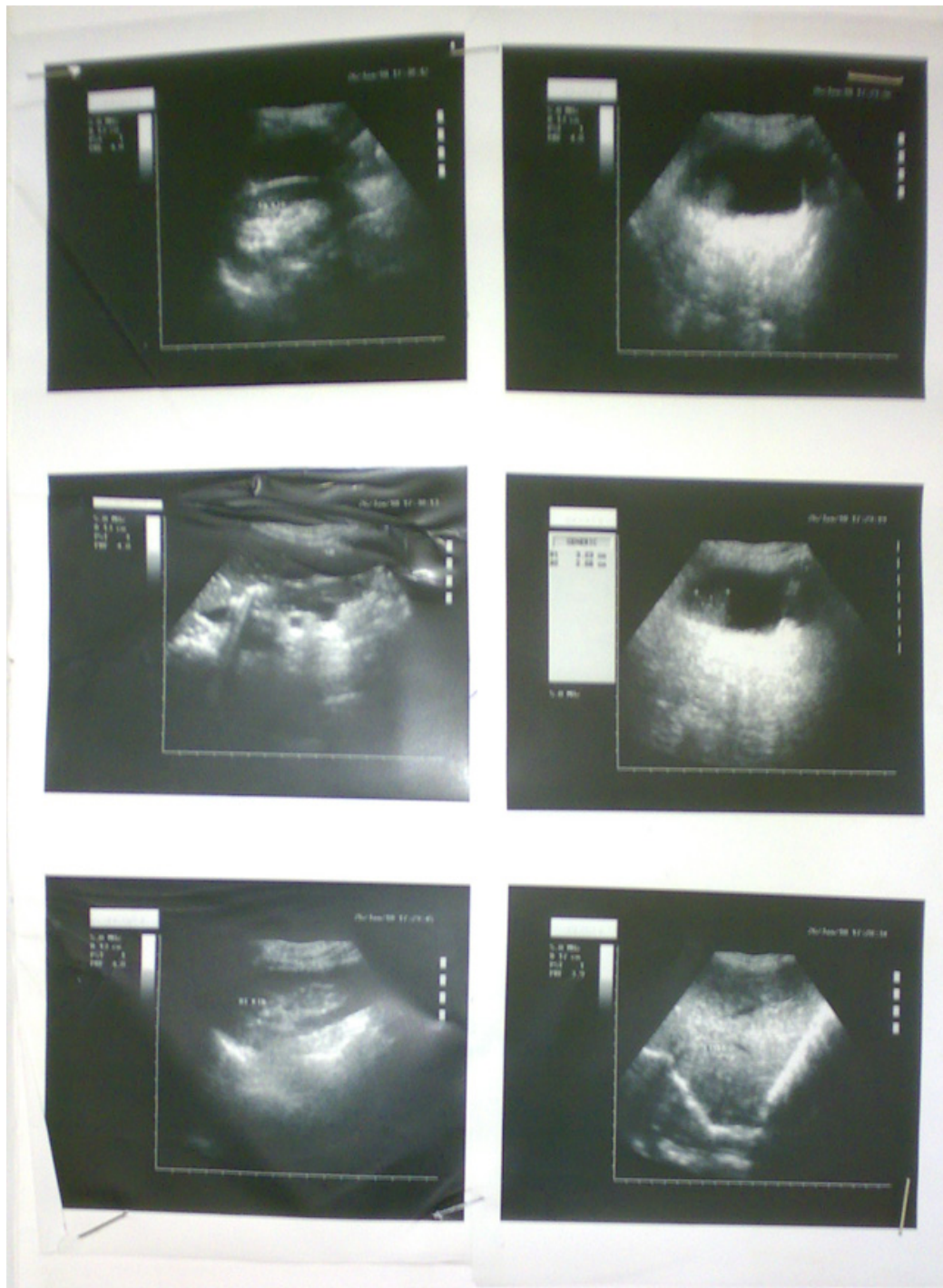
*PROSTATE :- is of average size showing homogenous echopattern, no focal lesions are detected.

*NO GROSS PELVIC MASSES ARE DETECTED.

CONCLUSION :-

- CHRONIC PARENCHYMAL LIVER DISEASE.
- URINARY BLADDER MASS.....FOR CYSTOSCOPY.

DR. TAREK FAWZY





Menoufia University
Faculty of Medicine
Pathology Department

Histopathology and cytology report

Code: 1117 path_No 140 /10 Category: نكحة الدولة Depar: المسالك البولية
Name: جابر عبد الحميد مرسى Age: 74 Sex: Male

Clinical data Urinary bladder mass.

Specimen TURP

Gross Picture: Multiple grayish white fragments collectively measured 2x2x2 cm, totally incubated.

Microscopic Picture: Sections examined revealed multiple bladder fragments infiltrated by ill-defined malignant growth formed of malignant urothelial cells arranged in sheets, clusters and strands that infiltrate the lamina propria and the included smooth muscle bundles. The malignant urothelial cells exhibited high degree of anaplasia in the form of marked pleomorphism, increase nucleo-cytoplasmic ratio, hyperchromatism, brisk mitosis and apoptosis. Area of high grade papillary transitional cell carcinoma could be detected. Multiple calcified bilharzial ova entrapped within neoplastic growth could be also seen

Diagnosis: TURP:
High grade transitional cell carcinoma associated with Bilharziasis invading the included muscle bundles.

pathologists

Prof.Dr: Dr. Nancy Asaad

Date of specimen receiving:

Dr: Dr. Asmaa Gaber

Date of signature:

صفحة 1

عبد الصالح
HEGAZY

Case II: Lupus Nephritis

Personal History:

- Mohammed Essam
- 12 years old

Complaint:

- Peri-orbital swelling since a month.

History of patient illness:

- The condition started since 1 month by sudden appearance of peri-orbital oedema then progressed to the whole face.
- The swelling is maximum in the early morning then decreases through the day. Then was no LL oedema.
- The patient made urine analysis, which showed identical microscopic hematuria & albuminuria.

System review:

- No hypertension
- No disturbance of consciousness.

Past history:

- No similar attacks
- No history of other diseases
- No operations.



A Picture of the case showing oedema



Some Investigations of Case 2

معمل ابن سينا للتحاليل الطبية

Date	17/01/10	ID No.:-	1145
Name	محمد عصام	Sex	
Referred By	د. محمد يحيى	Age	

Urine analysis

Physical Examination Normal

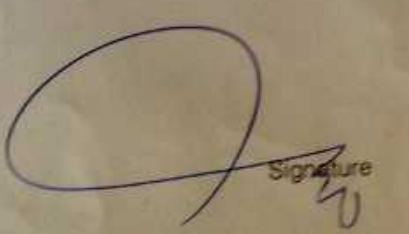
<u>Sample</u>	<u>Random sample</u>	
Volume	Sample	sample
Colour	Yellow	yellow
Aspect	✓ Turbid	clear
Reaction	Acidic	acidic
S. G.	1027	

Chemical Examination

		10 - 140 mg / day
Albumin	✓ +++	nil
Glucose	NIL	nil
ketones	NIL	nil
Nitrite	NIL	nil
Bile-pigments	NIL	nil
Bile-salts	NIL	nil
Urobilinogen	Normal Trace	nil

Microscopic Examination

		HPF
RBCs	✓ 75 - 80 (dysmorphic)	0 - 5
pus	✓ 16 - 18	HPF
Epithelial Cells	✓ +	HPF
Cast	✓ Granular +	
Crystal	NIL	
Amorphus	NIL	
Ova	NIL	
Other	NIL	



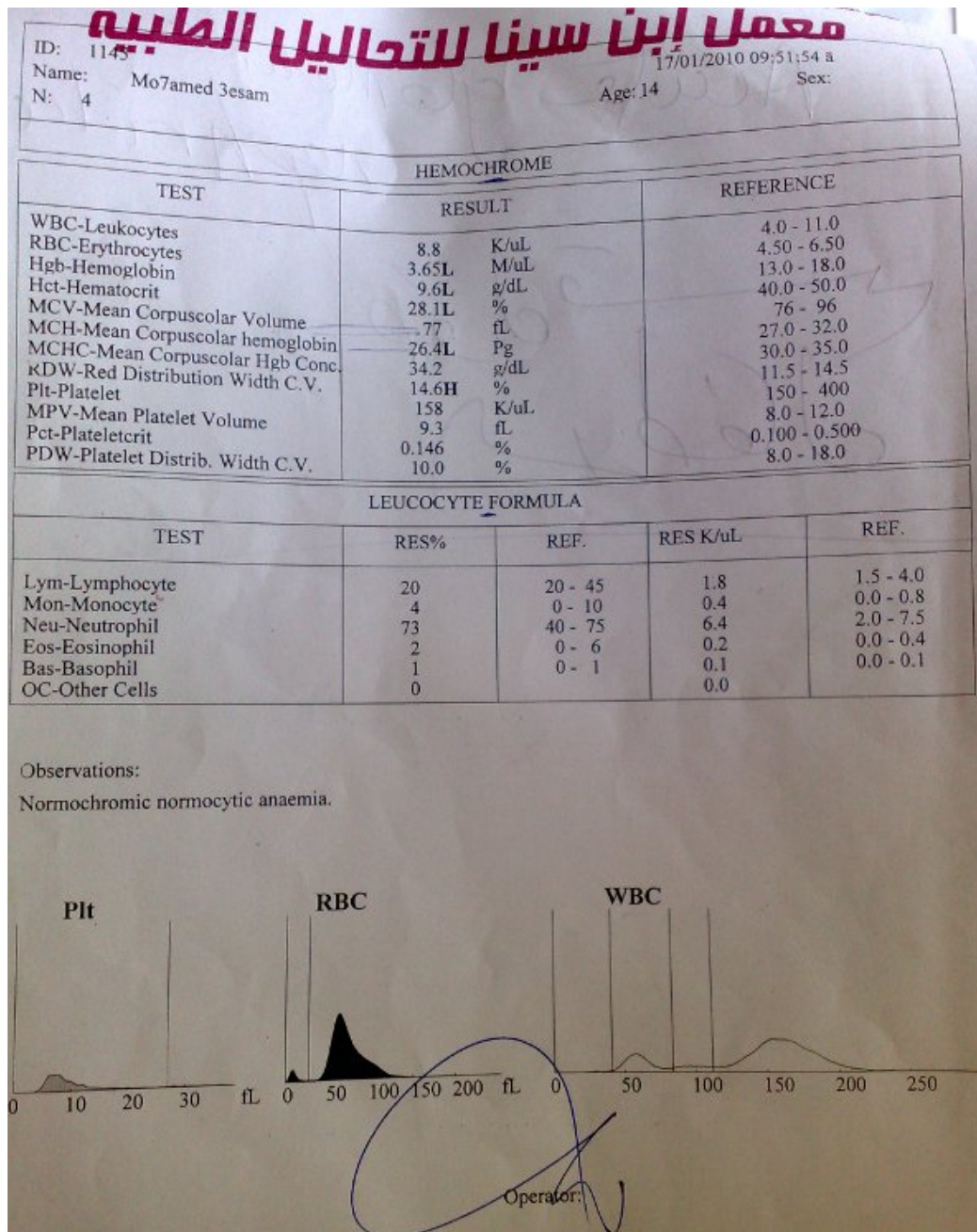
Signature

Report

Date 17/01/10 ID No.:- 1145
 Name محمد عصام Sex:-
 Referred By د محمد يحيى Age:-

TEST	Result	Normal
Albumin	2.3	g/dl 3.8 - 5.5
T.cholesterol	240	mg/dl 150 - 250
Prothrombin time		
patient	12.5	sec
control	12	sec
Activity.	92	%
INR	1.1	
urea	40	mg/dl 15 - 50
Creatinine	0.8	mg/dl 0.4 - 1.5

Signature



rws

MENOUFIA UNIVERSITY HOSPITAL
COAGULATION UNIT-HAEMATOLOGY

28/01/2010 - 12:51:01 Page 1

ANALYSES	RESULTS	CODE	NORMAL RANGE
1/28-7			
* prothrombin time 1	100 % 10.5 sec. 1.00 INR 12.9 Ref.T : To confirm :		70 ... 100 %
ALARM prothrombin time 1	Result		: value in primary units skewed

HEMATOLOGY Final Report 01/26/10 01:2

NAME: PAT#: AGE: SEX: U ORCOM: SAMPLE ID: 999
PCOM: DOC: /6.....
LOC:

TEST	RESULT	ABN	NORMALS	UNITS
WBC	10.36		(5.2 - 12.4)	10e3/ μ L
RBC	3.79		(4.2 - 6.1)	10e6/ μ L
HGB	9.9		(12 - 18)	g/dL
HCT	27.7		(37 - 52)	%
PCV	73.0		(80 - 99)	fL
MCH	26.3		(27 - 31)	pg
MCHC	36.0		(33 - 37)	g/dL
MCHM	37.4		(33 - 37)	g/dL
RDW	27.2		(-)	pg
RDW	14.7		(11.5 - 14.5)	%
RDW	3.82		(2.2 - 3.2)	g/dL
PLT	290		(130 - 400)	10e3/ μ L
MPV	10.5		(7.2 - 11.1)	fL
MICRO		++		
MC-VAR		+		
HYPER		+++		

NAME:
 PATIENT ID:
 AGE:
 DATE OF BIRTH:
 SEX: M
 LOCATION:
 PAT. COMMENT:
 SAMPLE COMMENT:
 INST CODES:

SAMPLE ID: 79
 SAMPLE TYPE: Serum
 DOCTOR:
 DRAW DATE/TIME:
 RUN DATE/TIME: Jan 22 10 17:17
 SEC/CUP/REP: 55/5

Handwritten: 2.4e3

CHEMISTRY	RESULTS	UNITS	REFERENCE RANGE	REMARKS
BUN	CAL TIME EXCEEDED			
AST	52	IU/L	10 - 42	HIGH
ALT	48	IU/L	10 - 42	HIGH
TGH	355	mg/dL	50 - 150	HIGH
ALBM	2.4	g/dL	3.5 - 5.2	LOW
CRER	0.7	mg/dL	0.4 - 1.4	
CHOH	146	mg/dL	150 - 250	LOW

☐ Provisional diagnosis:
☐ Remarkable clinical data :

☐ Fasting ☐ Lipaemia
☐ Haemolysis ☐ Unsuitable sample
☐ Jaundice

☐ Drug intake :
☐ Routine
☐ Same day
☐ Emergency

PLEASE CHECK IN THE REQUESTED TEST (S) IN BOX ONLY

Test	Result	Normal range	COMMENT
☐ Pregnancy test	:		
☒ ASOT	:	-ve	negative
☐ CRP	:		
☐ Rheumatoid factor	:		
☐ Paul Bunnell test	:		
☐ R . P . R	:		
☐ HBSAg	:		
☐ Toxoplasmosis	:		
☐ L . E . cell	:		
☐ Anti N . DNA	:		
☐ Widal	:		
	Typhi (O)		
	Typhi (H)		
	Para Typhi (A)		
	Para Typhi (B)		
☐ Brucella Test	:		
☐ Mone Spot Test	:		

Completed by : _____ Date : _____ Supervisor signature _____

IMMUNOLOGY , SEROLOGY

Case III: Benign Prostatic Hyperplasia

Personal History:

- Abd El-Hady Ismail Said
- 64 years old
- He was born & lives in Ashmoon.

Complaint:

- Reddish urine

History of patient illness:

- The condition started since ten days by appearance of blood in urine.

System review:

- No other systemic symptoms.

Past history:

- No DM
- No HTN
- No allergy.
- Rt. Hydrocelectomy 4 years ago.



الدراسات

جامعة المنوفية
مستشفيات جامعة المنوفية
طب وجراحة المسالك

مجانى	تأمين صحى وثيقة دولة أو تعاقبات	فندقى
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رقم المستشفى

التاريخ

كراسة علاج مريض بالقسم الداخلى

رقم التذكرة

استقبال

صفاة

قسم

عضو هيئة التدريس والطبيب المعالج

اسم المريض

محل الإقامة

الجنسية

عمر المريض

ذكر / أنثى

مرسل من

الديانة

صناعته

بيافادة رقم

ملاحظات طبيب العيادة أو الاستقبال

Hematuria BPH

حالة المريض عند الدخول

التشخيص المبدئى

الإمضاء	الإسم	مساء	صباحا	
No DM	Rt. hydrocelectomy	4 yrs ago		طبيب العيادة أو الإستقبال
No HTN	TRUS biopsy			حكيمة القسم
No allergy				الطبيب المقيم بالوحدة
Prost. Size 75 gm				
DRE ++ to +++				
PSA 12.09 ng/ml				

اسم

قاعة

مرفقات التذكرة

سرير

Pre 350

Post 200

Qmax 10.9

U/S: Rt. No BP

lt. BP, simple cyst

1

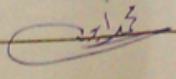
2

3

4

5

Some Investigations of Case 3

EXAMINATION SHEET				نموذج فحص	
الحجرة		القسم	تاريخ وساعة الخروج	تاريخ وساعة الدخول	اسم المريض :
			رقم المستشفى الموحد		
			عضو هيئة التدريس المعالج	الطبيب المقيم المناوب	
<u>Present History & Complaint:</u> male pt, 65 years with hematuria 10 days ago					
<u>Past History:</u> No DM No HTN No allergy					
<u>Family History:</u> Rt. hydrocelectomy 4 yrs ago					
<u>General Examination:</u> well					
<u>General Condition:</u> well					
Temp : 37 Pulse : 82 B.P : 110/70 Resp : 17					
Heart : free					
Chest : free					
Abdomen : lax, non tender, no scars					
<u>C.N.S.:</u> free					
<u>Musculo - Skeletal:</u> free					
<u>Genito - Urinary:</u> free					
<u>Others:</u> free					
<u>Local Examination:</u> Rt. hydrocelectomy scar					
<u>Provisional Diagnosis:</u> BPH					
Resident's Name :					
Signature :					

السن : ٢٠١٧ / ١ / ٢٤

م : السيد / عبد الله بن عبد الله

: م

URINE ANALYSIS

PHYSICAL EXAMINATION :

Volume/24hrs.	R.S	Sp. gr. :	
Colour :	Yellow	Odour :	
Reaction :	—	Deposits :	
Aspect :	Clear		

CHEMICAL EXAMINATION :

Albumin :	++	Sugar :	Nil
Acetone :	—	Bilirubin :	—
Urobilinogen :	—	Bile salts :	—
Nitrite test :	—	Haemoglobin :	—

MICROSCOPIC EXAMINATION :

Pus cells :	10 - 15	R.B.Cs. :	2 - 4
Epithelial Cells :	++	Ova :	—
Casts :	—	Parasites :	—
Crystals:	uric Acid +++	Mucus :	—
morphus :	—		

SUMMARY

Hematuria is a common symptom associated with many diseases. Whatever the circumstances, it should be regarded as a danger signal demanding immediate attention ⁽³⁴⁾. This research was a trial to cover some of the important aspects of hematuria. Additional information about any part of this research can be obtained by referring to our references below.



REFERENCES

- (1) Block B., Fervenza F., Pattison J., and Goldsmith D. "Membranoproliferative Glomerulonephritis". A Color Handbook of Renal Medicine. 2004. Page 34
- (2) Cooke R., and Stewart B. Color Atlas of Anatomical Pathology. Chirchill Livingstone, 3rd edition, 2004.
- (3) Elderderly A., et al. "Schistosomiasis in Sudan and beyond." Urologic Cancer. 3.4 (Dec. 2004): 18-20
- (4) El-Hindawi A. General Pathology. Cairo, 2009.
- (5) El-Hindawi A. Systemic Pathology. Cairo, 2009.
- (6) Esfahani T, and Hosseini M. "Association between idiopathic hypercalciuria and hematuria, nephrolithiasis or recurrent urinary tract infections in children." TUMJ. 57:B1 (1999): 28-33.
- (7) Fawcett D. "Bladder Cancer". ABC of Urology. Ed. Dawson C. and Whitfield H. Blackwell Publishing Ltd, 2nd edition, 2006.
- (8) Garcia C., Miller L., and Stapleton F. "Natural History of Hematuria Associated With Hypercalciuria in Children." Am J Dis Child. 145.10 (1991): 1204-1207.
- (9) Glasscock R. "Chapter 4: Hematuria and Proteinuria". Primer on Kidney Diseases. Elsevier Saunders, 4th edition, 2005. 36-41.



- (10) Glasscock R. "Chapter 28: Hematuria and Pigmenturia". Textbook of Nephrology - Volume 1. Baltimore/London: Williams & Wilkins, 1993.
- (11) Jennette J., and Heptinstall R. "Chapter 7: Membranoproliferative Glomerulonephritis". Heptinstall's Pathology of The Kidney – Volume 1. 6th edition, 2007. Page 254.
- (12) Kumar, Abbas, Fausto and Mitchell. Robbins Basic Pathology. Elsevier Saunders, 8th edition, 2007.
- (13) Kumar, Abbas, Fausto and Aster. Robbins and Cotran Pathological Basis of Disease. Elsevier Sauders , 8th edition, 2010.
- (14) Kumar, and Clark. "Chapter 11: Renal Diseases". Kumar and Clark Clinical Medicine. 6th edition.
- (15) Macfarlane P, Reid R., Callander R., and Govan A. Pathology Illustrated. Churchill Livingstone, 5th edition, 2000.
- (16) Mazhari R., and Kimmel P. "Hematuria: An algorithmic approach to finding the cause." Cleveland Clinic Journal of Medicine. 69.11 (Nov. 2002): 870-884.
- (17) Mcphee S. et al. "Chapter 22: Kidney Diseases". Current Medical Diagnosis. 48th edition, 2009. Page 10.
- (18) Mikuz G. Clinical Pathology of Urologic Tumors. Austria, Medical University Innsbruck.
- (19) Nada G. General Pathology Cairo: Al Ahram Press, 2009.



- (20) Nada G. Systemic Pathology Cairo: Al Ahram Press, 2009.
- (21) Nassef N. Medical Parasitology (Part I). 3rd edition, 2009.
- (22) Noble M. J. "Chapter 6: Hematuria". Essential Urology: A Guide to Clinical Practice. Ed. Potts J. M. Cleveland: Humana Press, 2004.
- (23) Olds R., and Dasarathy S. "Chapter 16: Schistosomiasis". Principles and Practice of Clinical Parasitology Ed. S. Gillespie, and Pearson R. John Wiley & Sons Ltd, 2001
- (24) Parmar M. "Microscopic Hematuria." The New England Journal of Medicine. 349.13 (Sep. 25, 2003): 1292
- (25) Riede U. , and Werner M. Color Atlas of Pathology. Thieme, 2004.
- (26) Sobh M. "Chapter 11: Miscellaneous." Nephrology For Medical Students.
- (27) Tam V. K. "An approach to microscopic hematuria." Hong Kong Practitioner. 17.J3 (July 1995): 309-312
- (28) Wiwanitkit V. "Pseudohematuria due to red dragon fruit ingestion." Chula Med J. 51.3 (Mar. 2007): 167- 71
- (29) Wu GY., et al. "Schistosomiasis: Progress and Problems." World Journal of Gastroenterology. 6.1 (Feb. 2000): 12-19.
- (30) Hematuria. 2009. Canadian Urological Assosication. <http://www.cua.org/documents/patient_information/05e-heme0109r.pdf>



- (31) Brayden R. Hematuria. 2007. McKesson Corporation.
- (32) Hematuria. Feb. 2007. National Kidney and Urologic Diseases Information Clearinghouse.
<<http://kidney.niddk.nih.gov/kudiseases/pubs/hematuria>>
- (33) What you should know about: Microscopic Hematuria. May 2006. American Academy of family physicians.
<<http://www.med.wright.edu/medpeds/patients/Pt%20Ed%20Microscopic%20Hematuria.pdf>>
- (34) Rajaratnam E. Hematuria. <www.drrajmd.com>
- (35)< <http://emedicine.medscape.com/article/437096-overview>>
- (36) Karnath B., Rodriguez G., and Narat R. Evaluation of Hematuria
- (37)<<http://www.urmc.rochester.edu/urology/adult-patients/hematuria.cfm>>
- (38)<<http://www.medicues.com/conditions/hematuria>>
- (39)<<http://www.medterms.com/script/main/art.asp?articlekey=6806#>>
- (40)<<http://www.cancerhelp.org.uk/type/kidney-cancer/about/symptoms-of-kidney-cancer>>
- (41)<<http://www.AUAFoundation.org>> The American Urological Association Foundation
- (42) Bladder cancer. UK incidence statistics



(43) < <http://en.wikipedia.org/wiki/Glomerulonephritis>>

(44)<http://wrongdiagnosis.com/symptoms/urine_color_changes/book-causes-5b.htm>

